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OBSERVATIONS UPON THE ETIOLOGY OF TUMORS.¹

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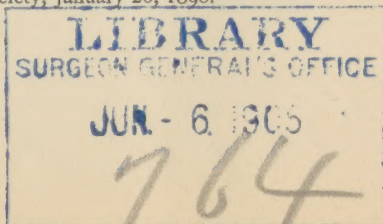
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ONE of the manifold duties devolving upon the surgeon is the assumption of the *rôle* of managing agent in the study of what we class to-day under the head of *tumors*. He comes in contact with the patient before, during, and after the operation, and should suggest the various investigations to be made, in order to definitely determine the nature of the growth. Yet he to-day seems to be entirely engrossed in the limited sphere of the enucleation of the mass, apparently wishing to leave to any one its examination, and frequently satisfying himself with an account, based upon the arrangement and character of cells taken from a small section of the tumor. He should take a higher position in this matter, and should direct the disposition of the tumor to the proper channels for investigation, being alive to the knowledge embraced in the anatomy, embryology, teratology, histology, pathology, and bacteriology, in so far as they may have reference to the growth. I firmly believe that if the surgeon would act in this capacity, a great deal of material now wasted would be intelligently utilized, and that our views in regard to tumors would be greatly modified or completely changed in the next few years.

In a purely clinical aspect, certain tumors appear during intrauterine life, being present at birth, or manifesting themselves first during childhood or adolescence. Among these

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may be mentioned some osteomata, chondromata, fibromata, adenomata, and heterologous tumors in or near the kidney, parotid gland, testicles, or brain.

A certain number, again, appear to follow inflammation, especially when it is accompanied by cicatrization or ulceration. Such tumors may be seen in the larynx, at the pyloric end of the stomach, in the gall-bladder, and at the site of the tubercular and syphilitic granulomata.

A certain number, again, seem to follow an injury or injuries. This influence appears to be present in about 7 to 18 per cent.

The atrophy of tissue elements has apparently an influence in the development of cancer, in that it lessens or removes certain opposing forces to its advancement, just as heredity, the want of resistance or predisposition to tumor-formation appears to exist in from 5 to 15 per cent. of the cases of malignant disease. (The value of statistics in heredity must necessarily depend upon the care of the investigator and the intelligence and knowledge of the patient.) This is the purely clinical aspect under which we meet tumors. The theories of the origin of tumors, however, must be considered, in order to appreciate the drift of the thought expended upon the solution of this question.

In the Cohnheim theory, no other cause is recognized than a failure in the embryonal deposit,—that is, an excessive production of cells in an early stage of embryonal life, which cells are not completely utilized in the formation of the tissue. Trauma can convert such a benign or unrecognized new growth into a malignant one, but it cannot, of itself, produce a tumor.

Virchow places the cause in local disturbances, hereditary or acquired in later life, as the result of trauma or pathological processes (inflammation and ulceration). These conditions may not only favor but give rise to a new growth.

That mechanical or chemical insults were able to produce the necessary local disturbance was not admitted by Billroth. He distinctly maintained that something else was

necessary,—namely, a specific “disposition of the individual.”

Lücke maintains that local irritations and injuries, especially mechanical, are only occasioning causes, and that greater importance is to be ascribed to the general predisposition of the individual.

Löwenthal, who collected some 800 cases of tumor-formation, believes that the majority furnish enough proof to suppose that external irritation can occasion a tumor, in that it involves cell elements not utilized in normal tissue-formation or other tissues are involved which react abnormally.

Löwenthal's 800 cases comprise 316 sarcomata, in 287 of which the kind of trauma was known. Liebe, in 343 cases, found that trauma preceded the development of the growth in 10.8 per cent.; Wolff, in 574 cases, in 50 per cent.; Gross, in 165 cases, in 14.3 per cent. Wild, in 423 cases, found fifteen cases in which a single severe blow preceded the development of the growth. Kirchner, in 76 cases of sarcoma, found ten cases in which trauma preceded the appearance of the tumor. Tillmann has collected 499 cases of malignant tumors, comprising 328 carcinomata and 171 sarcomata. Of the 328 carcinomata, thirty-five developed after a single blow, and ninety-two followed upon chronic irritation. Of 171 sarcomata, thirty-five followed a single blow, and thirty-two developed upon a chronically irritated area. In the whole number (499) we have ninety cases following a single blow (18 per cent.) and 124 developing upon a chronically irritated area (25 per cent.). This summary substantiates the theory of Virchow, as well as the commonly accepted view, that sarcoma is more frequently referred to a single blow, while carcinoma is referred more often to chronic irritation. Sarcoma: 20 per cent. to injury; 19 per cent. to chronic irritation. Carcinoma: 11 per cent. to injury; 28 per cent. to chronic irritation.

It is the belief of Ribbert that tumors arise before and after birth from a partial or complete separation of cells or groups of cells from their organic connection. The cells

withdrawn from the influence of a cell association of their own, where they maintain a vegetative activity, and are situated in a tissue suitable for their growth, grow and form tumors similar or dissimilar to the organ from which they arise.

Chondromata may thus arise from anomalous ossification of the epiphyses of bones, sarcoma from the periosteum or medulla of bones, epithelial or epidermoidal tumors from the epidermis. The cell groups may be separated from their association by traumatism or connective-tissue contraction. They may likewise be due to foetal displacement of cells, either connective tissue or epidermis.

Hauser maintains that the theory of a simple misplacement of cells producing a tumor is not proven by Ribbert, at least for the carcinomata, since this can only depend on fundamental change in the biological and morphological properties of epithelial cells, giving them a distinct biological and morphological difference from the mother cells. This unknown agent or factor, Hauser maintains, probably exists in the connective tissue, and exerts itself first upon the epithelial cells, just as a simple atypical epithelial growth is derived from pathological processes in connective tissue. Scheurlen and others have found harmless saprophytes, as well as staphylococci, streptococci, and bacilli, in the foci where softening was taking place in a tumor. Zahn, Hauser, and Ribbert have shown them to exist in tumors not exposed to the air. These are, however, of no importance, since all tumors due to the schizomycetes are formed of granulation tissue, and consist of leucocytes and young connective tissue, whereas all metastases of carcinoma consist essentially of epithelioid cells similar to the focus.

Darier, Albarran, Malassez, Thoma, and Wickham believe in the parasitic origin, and attempt to prove that carcinoma is due to protozoa, especially the sporozoa. The views expressed by them are not satisfactory nor similar, contradicting one another, not only in their frequency, but also in their form and character.

Adamkiewicz and Pfeiffer consider the carcinoma cell the specific parasite, and not a derivative of other cells. The protozoa, as a cause of carcinoma, Hauser considers of no avail, since only in malaria, and in the intracanalicular papilloma of the biliary ducts, and in a few diseases in animals, has the proof been incontestable. Possibly, though not completely, proven is their causal relation to *molluscum contagiosum* and dysentery.

Schwartz also criticises severely the protozoan theory, and the extreme views of Adamkiewicz and Pfeiffer. From investigations made upon absolutely fresh preparations, he believes all these cell-inclusions are degeneration products of epithelial cells, leucocytes, and their derivatives.

Maffucci and Sirleo deny any pathogenic properties existing in the blastomycetes of Sanfelice and others. From personal observations they are led to believe that the blastomycetes produce a chronic inflammatory process, such as a new formation of tissue, but not tumors, either carcinomata or sarcomata.

The theories of the etiology of tumors give us but little definite knowledge, beyond the possible causes, yet the advances in later years in pathological histology, embryology, and bacteriology have aided our knowledge, and allowed us to at least restrict the term.

Virchow first separated the infectious granulomata from the tumors, and they were subsequently shown to be due to micro-organisms. The leprous nodule, the farcy nodule, the tubercular gumma, actinomycosis, and possibly the syphiloma. Then the hydatid cysts were restricted to the cystic stage of the *tænia echinococcus*.

Cohnheim's theory of the origin of tumors was the great incentive to the investigations into the "vestiges" and "rests,"¹ and has led to a thorough study of embryology and teratology, restricting again the number, and including many under the congenital malformations.

In the non-epithelial tissues, such rests are difficult to demonstrate. Isolated islets of cartilage have long been

known to exist in the epiphyses of rachitic children, and, it is probable, as Ricker and Sutton suggest, that some uterine myomata are sequestered portions from the union of the Müllerian ducts. Von Recklinghausen, indeed, considers some adenomata and cystomata of the uterus as rests from the Wolffian body. Birch-Hirschfeld places the origin of some adenomata of the kidney among the rests from the Wolffian body, while Grawitz maintains that some of them are due to sequestered portions of adrenal tissue. These and other well-known instances of cysts and cyst-adenomata, due to a glandular rest or vestige, and not to trauma, inflammation, or a parasite, will allow us to again restrict the term.

Many lymphadenomata and so-called lymphosarcomata have likewise been taken from the tumor list, and classed as varieties of tuberculosis, leukæmia, pseudo-leukæmia, or as diseases *sui generis* (malignant lymphoma).

The rhinoscleroma, the *molluscum contagiosum*, the mycosis fungoides (Alibert), and certain enlargements of the thyroid gland, especially where combined with cretinism, have, of late, been placed among the disturbances of nutrition or the infectious processes, though formerly recognized as true tumors.

The tumors which do not apply to the theory of vestiges, rests, and teratological formations, nor alone to an inflammatory process nor traumatism, are the sarcomata and carcinomata.

Many facts indicate that cancer is induced by minute organisms, since, by analogy, in origin, course, and constitutional involvement, it is similar to those diseases which we know to be parasitic in origin, as well as the fact that those organs and glands which are in contact with the air and intestinal gases are the most prone to cancer,—*e.g.*, the breast, the rectum, the stomach, and the cervical canal of the uterus, in contradistinction to the body of the organ.

The same view is held of sarcoma, yet they are not believed to be due to the same cause, nor can the varieties of each even be said to depend upon a single cause, simply

because of the structural likeness, for, as Virchow remarks, no neoplasm contains cells which are, in a strict sense, specific to it.

The cells of the peritoneum have been variously looked upon as endothelial and epithelial. In the infectious diseases, syphilis, leprosy, and tuberculosis, we also find peculiar cells, giant-cells, "Mastzellen," and epithelioid, derived from connective tissue, and often indistinguishable from epithelial cells. This is shown by Schöbl, and more recently by Volkmann, Jr., in the endotheliomata.

Quincke and Rieder attempted to establish the fact that carcinoma cells in exudates (pleural and peritoneal) might be distinguished from endothelial cells by the large number of mitoses, especially asymmetrical division forms, and by their glycogen reaction. From the fact that endothelial cells in effusions exhibit such a diversity in size and shape, and show a similar vacuolation, fatty degeneration, and often abundant mitoses, many investigators declare it impossible to differentiate them from carcinoma cells, unless definite bits of tissue, showing a definite structure, can be examined. The possibility, then, of the secondary deposit in cancer having its cells develop by growth and differentiation of indifferent connective-tissue cells may be true (Virchow, Gussenbauer, Stricker, Klebs), for the rule that so-called epithelial cells can only be derived from epithelial cells may be true for normal conditions, but not for pathological ones.

But we cannot verge too far in the tendency to disregard the genesis, character, and the relation of cells to the tissue in which carcinoma and sarcoma develop, for it is a fact that the cells of both depend, for the greater part of the tumor, upon the nature of the parent tissue from which they develop ("*omnis cellula e cellula ejusdem generis*," Thiersch and Waldeyer), although the new cells possess distinctly different morphological and physiological characters from those of the cells from which they take their origin. There exists certainly a fundamental biological difference between the metastases of malignant tumors and those of

infectious diseases, in that in one micro-organisms and in the other the cells (so far as we know) represent the means of extension of the disease. The biological process and the anatomical conditions cannot be combined to substantiate at the present time the parasitic theory. The constant failures in inoculating animals may appear at first as evidence against a parasitic theory, yet we know the same condition exists in other undoubted infectious diseases, as leprosy and syphilis.

It is probable that trauma exerts a primary influence in some retention cysts, implantation cysts, in some so-called cystic adenomata, as well as probably in some fibromata, lipomata, enchondromata, and osteomata. This may be seen in many of the simple retention cysts, in epidermoidal cysts, in the cystic tumors of the breast, involving the ampullæ and larger ducts (Nasse), as well as in some fibromata and lipomata, enchondromata, and osteomata following injury to connective tissue or bone.

The injury in this case probably induces a *locus minoris resistentiæ*, in that in the disorganization of the tissue vessels are closed, the circulatory character is changed, and an occasion for the deposit of tissue elements is given, which either develop into scar tissue, and produce by the obliteration of ducts retention cysts and the so-called cystic adenomata, or by the enclosure of abnormal elements, where they maintain a vegetative activity (Ribbert), epithelial, fatty, and connective-tissue tumors (benign).

Injury in sarcoma and carcinoma is, I think, an occasioning cause, and is generally expended upon tissues, the result of congenital rests or inflammatory processes. In those in whom these conditions do not exist, we must accept either a general predisposition in the individual or a local disturbance in nutrition, evidenced by a deranged functional activity in the cells, with the production of chemical toxins or by the presence of micro-organisms with their ptomaines. The predisposition cannot be denied absolutely, although one would expect to see more cases of multiple sar-

comata and carcinoma in those who have either variety, since injuries will constantly occur in such persons. In such cases of multiple tumors of this variety, they can generally be explained by metastasis, by direct implantation, by congenital defects, and, rarely, by multiple injuries alone. The presence of both carcinoma and sarcoma in the same individual must be looked upon as a purely accidental condition. The injury acts as an occasioning cause, and is followed by a parasitic infection or by a disturbed functional activity in the cells of the injured tissue with the development by these cells of toxins. The primary cause of this deranged functional action in the cells must remain unknown until the biology and chemistry of cell-action are better understood. Congenital formations, the new formations following inflammation, and, in some individuals, injury alone, seem to be predisposing agents in developing this deranged functional activity.

Inflammation, used in a broad sense (disturbed nutrition), acts as a primary cause in many so-called tumors. As an interstitial process, it causes by its scar tissue the obliteration of ducts and the formation of retention cysts and the so-called cystic adenomata. As a parenchymatous process, involving the epithelium alone, and not extending beyond the membrana propria, it causes the multiple and circumscribed cystadenomata, proliferating cystadenomata, by a process both parenchymatous and interstitial, some so-called adenofibromata (Nasse). These simple hyperplastic glandular processes, if they follow inflammation and ulceration, as in the intestine and uterus or breast, are considered as evidences of reproductive activity, following, in the main, the pattern of the gland, but really appearing as an atypical glandular formation.

If the signs of inflammation are wanting, or slightly marked, they are considered as hypertrophic productions from an unknown cause. These atypical glandular growths should not be confounded with true adenomata, for they often belong among the regular phenomena of a distinct

diseased condition. True adenomata are by no means common, and if we exclude the adenocarcinomata and the cyst-adenomata, they may be properly considered as sequestration adenomata, such as occur in the liver, spleen, kidney, and broad ligament from adrenal implantation in the uterus from sequestered portions of the Wolffian body, etc.

Inflammation, again, offers an occasioning cause for a great number of carcinomata, as carcinoma and leucoplakia (Schuchardt), carcinoma and paraffin dermatitis; facial cancer and chronic seborrhœa, Paget's disease, and the eczemata, carcinoma and syphilitic ulceration, carcinoma and lupus; carcinoma engrafted upon tubercular cavities in the lung, carcinoma developing upon the scars of burns and former ulcers.

Fully 70 per cent. of all malignant tumors develop upon the most maltreated and frequently inflamed organs. The stomach, 34.97 per cent.; the breast, 4.3 per cent.; the uterus and vagina, 18.5 per cent.; the large intestine and rectum, 8.1 per cent.; the face and lips, 4.9 per cent.

It is probable that the diseased tissue either offers the atrium for micro-organisms, which, slow in growth, are only able to develop upon ill-nourished tissues, or that the nutritive disturbance in the tissue cells results in a deranged functional activity, with the production of chemical toxins.

The third cause we consider the congenital anomalies, either the misplacement of germinal fragments or the remains of foetal formations. They include the cysts of former canals or ducts, the vascular and lymphatic growths, the adenomata, the epithelial and connective tissue rests, as well as the endogenous and ectogenous teratomata.

As cysts, we find the tubulodermoids, the ovarian dermoids, the tubulocysts, and the neural cysts. As adenomata and rests, the adenomata of the pituitary gland of the accessory thyroids, and of the ovary, the sequestration dermoids, the adrenal implantations in the kidney, liver, and broad ligaments of the Wolffian body in the kidney and uterus, as well as many fibromata and enchondromata. Here might also be

mentioned the elephantiasis congenita, the plexiform and multiple neurofibromata, and the multiple exostoses and enchondromata.²

As vascular and lymphatic growths, the hæmangioma simplex and cavernosum, the angioma arteriole racinosum, the lymphangioma simplex and cavernosum.

As teratomata may be mentioned, the parasitic foetus, and the tumors developed from imperfect anterior and posterior dichotomy. We would place the carcinoma and sarcoma in a separate class of disturbances in nutrition, which have for their cause or causes unknown agents. We do this because of the fact that the analogy between malignant tumors and infectious diseases is rendered incomplete, owing to the character of the metastases, but we do not lose sight of the fact that in all other points they agree, and that the apparent antagonism between the anatomical conditions found in malignant tumors and the biological process, may be dependent on our own inadequate knowledge and methods of investigation.³

Lubarsch goes so far as to say that every new growth in case elements of the same enter the blood and lymph-channels, and the resorptive power of the body is diminished, has the power to cause metastases.

We admit that certain enchondromata, adenomata of the thyroid, of the liver, biliary passages, and myomata or adenomata of the uterus, stomach, and intestines, have been reported as having metastases, but we can hardly consider this fact as militating against the specific characters of carcinoma and sarcoma, when compared with benign tumors. We all know that many glandular formations in mucous membranes and within glands (simple and hyperplastic) cannot be differentiated from true adenomata, just as some adenomata cannot be distinguished from adenocarcinomata. It, indeed, becomes a matter of the individual judgment alone whether the investigator places the growth in the one or the other class.

This is especially the case in the intestinal tract, where

adenomata, which should be classed tubular adenomata, show a marked malignancy by their extension in the surrounding tissues, and not infrequently are followed by metastases. If we judged these growths by their purely histological characters, we call them adenomata; if by their course and behavior to the surrounding tissues, carcinomata,—that is, adenocarcinomata.

So also in the enchondromata, we know that where the tumor is represented by a distinct and genuine cartilage, it is a benign growth, and that in certain cases only, where the cartilage represents probably a purely transitional tissue, do we find metastases, unless it be that an injury or repeated injuries to a benign enchondroma have been followed by sarcomatous degeneration.

In the myomata as well, we are satisfied that a pure example of such a growth is a distinctly benign process, whereas when the growth contains cells which can be distinctly recognized as muscle-fibres, and, in addition, cells which have no specific character, it becomes a myosarcoma, and may cause metastases.

In fifty-one cases of mixed congenital growths of the kidney in children (Walker) the metastases were of a sarcomatous nature in all excepting one instance, in which striped muscle-fibres were found in what was thought to be a metastatic nodule in the diaphragm.

In a case of teratoma colli, in a child of nine weeks of age, Popovac described the growth as consisting of embryonal tissue, with changes towards higher types of tissue, bone, cartilage, striped and unstriped muscular tissue, as well as of glial tissue and ganglion-cells. In three distinct nodules removed from the neighborhood of the main growth, and which Popovac considered lymph-glands because of their capsule and the lymphoid tissue beneath the capsule, he found the same embryonal tissues together with the glial tissue, but without the ganglionic cells. The question, in this case, seems to be whether Popovac has fully proven the outlying nodules to be lymphatic glands. If so, we must ex-

plain this fact by the inherited power of transplanted cells to develop after their own type up to the time that their characters and function are completely altered by their environment (Sarcoma).

If these nodules do not represent glands, then we are to consider the case as one of multiple teratomata in this region.

The constitutional effects produced by both carcinoma and sarcoma may be due, in part, to the degeneration and ulceration of the tumor, by means of which large amounts of albuminous material are lost, as well as to the putrefactive processes within the tumor, by which injurious substances act upon the system. The probability that malignant tumors, when the above conditions do not exist, develop substances (toxines) which act upon the tissues of the body cannot be denied. We know that, independently of organisms, cells, both in animals and man, possess the power of producing chemical products which react upon the metabolism of the tissue. All that takes place within the body is closely associated with cell-action, and that this action is purely a chemical one is beyond question. The details of the normal tissue-changes and the chemistry of the action of the cells we do not understand sufficiently to be conversant with their pathological changes. We see only the results of these abnormal changes, but do not know their source nor nature.

We include here the epithelial cancers (flat and cylindrical celled), the carcinoma simplex, and the scirrhous and the alveolar carcinoma.

In the sarcomata we include the spindle-, round-, giant-, and mixed-celled sarcomata, the melanosarcoma, the endothelial sarcoma, and the lymphosarcoma. The varieties of carcinoma, as of sarcoma, depend upon the nature of the parent tissue from which they originate, and it is our duty to investigate the character, shape, and arrangement of the cells, in so far as they give us a definite idea of the probable origin of the growth, and its method of extension along or into the lymphatic spaces, lymphatics, the veins, and the ducts of glands.

The morphological and physiological properties of the cells of malignant tumors are very different from those of the mother cells, and it is again demanded of us to inquire into the nature of the agent or agents which impart to the cells these new properties.

Our right to place the malignant tumors among the disturbances of nutrition is quite as tenable as to consider syphilis, malignant lymphoma, leukæmia, and pseudo-leukæmia in the same class. In neither is the cause known, and in all the supposition is that the agent producing them is the result of cellular action, with the development of leucomaines or ptomaines.

With the continued investigations in the study of our so-called tumors, I believe that surgery is destined to be relieved of the nomenclature and classification which we now employ, and a classification in which the primary cause will be the criterion will place our tumors:

(1) As the results of traumatism.

(2) As the results of inflammatory processes, especially those followed by cicatrization and ulceration,—*i.e.*, a local disturbance in the nutrition of a part.

(3) As the results of congenital anomalies.

(4) As the results of disturbances in nutrition, due to toxines, chemical or possibly parasitic, developed most frequently upon a soil prepared by traumatism, inflammation, or a sequestral anomaly.

The observations made and the deductions drawn from them in this paper are such as have impressed themselves upon me in an attempt to combine the pre- and postoperative clinical history of tumors with the macroscopical and microscopical reports of the pathologist. Though I may be completely in error, I nevertheless, in order to develop an interest in the subject, give my views in reference to tumors or neoplasms, using the term as it is employed in our surgical works.

REFERENCES.

¹ The "vestige" is a remnant of an organ functional in vertebrates lower than man, of an organ important to the embryo, but useless to man, of an organ utilized in one sex and not in the other, and of structures useful to our progenitors, but not in any distinct or existing vertebrate, mesonephros,—Gärtner's parovarium, etc. A "rest" refers to a detached fragment of a gland or isolated portions of a tissue or epithelium, as the accessory thyroids, adrenal implantations in the kidney and broad ligament, etc.

² Multiple cartilaginous exostoses and enchondromata represent a disease of itself, and is due to a disturbance in the intermediary cartilage from an original failure in perfect growth based upon nutritive disturbances in the bones involved, and in the rest of the skeleton as well. Bessel-Hagen first referred to the general skeletal changes, and Nasse and von Bergmann have substantiated it.

³ Lipomata, multiple and symmetrical, as well as neuromata, multiple and symmetrical, when not congenital (at least, where no data to that effect exist), are considered trophoneurotic. Should these facts be true, these conditions would be placed among the disturbances in nutrition, due to trophic influence, and not considered as the result of congenital defects in perfect growth.

